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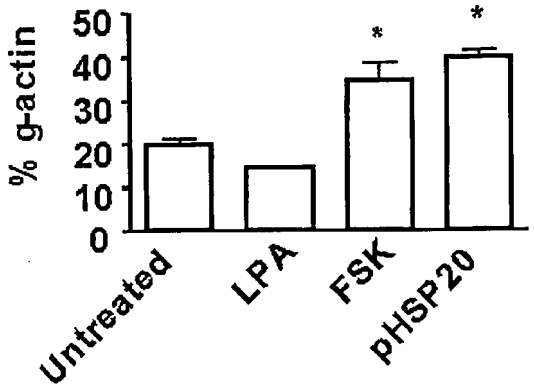
(54) Title: METHODS FOR PROMOTING WOUND HEALING AND/OR REDUCING SCAR FORMATION



PhosphoHSP20 peptide disrupts the actin cytoskeleton.

(57) Abstract: The present invention provides methods for promoting wound healing and/or reducing scar formation, by administering to an individual in need thereof one or more of the heat shock protein 20-derived polypeptides disclosed herein.

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METHODS FOR PROMOTING WOUND HEALING AND/OR REDUCING SCAR FORMATION

Cross Reference

This application claims priority to U.S. Provisional Patent Application Serial Nos. 60/448,954 filed February 21, 2003; 60/512,211 filed October 17, 2003; and 60/530,306 filed December 16, 2003, each of which is incorporated by reference herein in its entirety.

Field of Invention

This invention relates generally to methods for promoting wound healing and inhibiting scar formation.

Statement of Government Rights

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Background of the Invention

The primary goal in the treatment of wounds is to achieve wound closure. Many wounds routinely heal by a process which comprises six major components: i) inflammation, ii) fibroblast proliferation, iii) blood vessel proliferation, iv) connective tissue synthesis v) epithelialization, and vi) wound contraction. Wound healing is impaired when these components, either individually or as a whole, do not function properly. Thus, therapeutics that provide a benefit to any of these components provide a benefit to the wound healing process.

During wound healing, cells, including fibroblasts, migrate into the wound area. These cells form stress fibers and focal adhesions that serve to help close the wound during the wound contraction step. While wound contraction is an essential component of wound healing, the development of scar contractures in tissues and organs disrupts normal organ integrity and produces functional deformities. Limiting wound contraction during the wound healing process allows the surrounding tissue more time to regenerate and heal with reduced scarring. Thus, compounds that limit wound contraction can be used to reduce scar formation that accompanies wound healing.

It has recently been determined that cyclic nucleotide-dependent relaxation of vascular smooth muscle is associated with an increase in the phosphorylation of the small heat shock related protein 20 ("HSP20"). HSP20 is highly and constitutively expressed in muscle tissues and can be phosphorylated in vitro by cGMP-dependent protein kinase. HSP20 has been shown to associate with actin and α-actinin, a focal adhesion protein. Activation of cyclic nucleotide dependent signaling pathways also leads to a decrease in the association of HSP20 with α-actinin, suggesting that HSP20 may lead to relaxation of vascular smooth muscle through a dynamic association with cytoskeletal proteins.

However, the role of HSP20 and peptides derived therefrom in modulation of wound healing and scar formation responses is not known.

Summary of the Invention

The present invention provides methods to promote wound healing and/or reduce scar formation, comprising administering to an individual in need thereof an amount effective to promote wound healing and/or reduce scar formation of one or more polypeptides comprising a sequence according to general formula I:

X1-A(X2)APLP-X3

wherein X1 is 0-14 amino acids of the sequence of heat shock protein 20 between residues 1 and 14 of **SEQ ID NO: 298**;

X2 is selected from the group consisting of S, T, Y, D, E, hydroxylysine, hydroxyproline, phosphoserine analogs, and phosphotyrosine analogs; and

X3 is selected from the group consisting of (a) 0-140 amino acids of heat shock protein 20 between residues 21 and 160 of **SEQ ID NO:298;** and (b) 0, 1, 2, or 3 amino acids of a sequence of genus Z1-Z2-Z3, wherein Z1 is selected from the group consisting of G and D;

Z2 is selected from the group consisting of L and K; and

Z3 is selected from the group consisting of S, T, and K.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: PhosphoHSP20 peptide disrupts the actin cytoskeleton. 3T3 cells were cultured and treated as indicated on the graph (*4*). Monomer g-actin was biochemically quantitated using a DNase 1 inhibition assay. The level of g-actin in the cell extract that

caused 50% inhibition of DNase 1 was estimated from a standard actin curve that was determined using known amounts of actin. * $P < 0.05$ compared to untreated cells.

Figure 2: FITC-phosphoHSP20 peptide disrupts focal adhesions. Results from the focal adhesion assay using interference reflective microscopy on 3T3 cells treated as described (*4*). Each condition was tested in triplicate, and an average of 250 cells per coverslip was counted. A cell was scored positive if it contained at least five focal adhesions. Hep I (peptide from thrombospondin 1) was used as a positive control. * $P<0.05$ compared to untreated cells.

Detailed Description of the Invention

All references cited are herein incorporated by reference in their entirety.

Within this application, unless otherwise stated, the techniques utilized may be found in any of several well-known references such as: *Molecular Cloning: A Laboratory Manual* (Sambrook, et al., 1989, Cold Spring Harbor Laboratory Press), *Gene Expression Technology* (Methods in Enzymology, Vol. 185, edited by D. Goeddel, 1991. Academic Press, San Diego, CA), "Guide to Protein Purification" in *Methods in Enzymology* (M.P. Deutshcer, ed., (1990) Academic Press, Inc.); *PCR Protocols: A Guide to Methods and Applications* (Innis, et al. 1990. Academic Press, San Diego, CA), *Culture of Animal Cells: A Manual of Basic Technique, 2nd Ed.* (R.I. Freshney. 1987. Liss, Inc. New York, NY), *Gene Transfer and Expression Protocols*, pp. 109-128, ed. E.J. Murray, The Humana Press Inc., Clifton, N.J.), and the Ambion 1998 Catalog (Ambion, Austin, TX).

The single letter designation for amino acids is used predominately herein. As is well known by one of skill in the art, such single letter designations are as follows:

A is alanine; C is cysteine; D is aspartic acid; E is glutamic acid; F is phenylalanine; G is glycine; H is histidine; I is isoleucine; K is lysine; L is leucine; M is methionine; N is asparagine; P is proline; Q is gluatamine; R is arginine; S is serine; T is threonine; V is valine; W is tryptophan; and Y is tyrosine.

As used herein, the singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise. For example, reference to a "polypeptide" means one or more polypeptides.

In one aspect, the present invention provides methods for promoting wound healing and/or reducing scar formation comprising administering to an individual in need

thereof an amount effective to promote wound healing and/or reduce scar formation of a polypeptide comprising or consisting of a sequence according general formula I:

X1-A(X2)APLP-X3

wherein X1 is 0-14 amino acids of the sequence of heat shock protein 20 between residues 1 and 14 of **SEQ ID NO: 298**;

X2 is selected from the group consisting of S, T, Y, D, E, hydroxylysine, hydroxyproline, phosphoserine analogs, and phosphotyrosine analogs; and

X3 is selected from the group consisting of (a) 0-140 amino acids of residues 21 and 160 of **SEQ ID NO:298;** and (b) 0, 1, 2, or 3 amino acids of a sequence of genus Z1-Z2-Z3, wherein Z1 is selected from the group consisting of G and D;

Z2 is selected from the group consisting of L and K; and

Z3 is selected from the group consisting of S, T, and K.

Residues 15-21 from HSP20, with possible substitutions at residue 16 of HSP20 form the structural core of the polypeptides according to general formula I (A(X2)APLP) **(SEQ ID NO: 2)**. The full sequence of HSP20 is provided as SEQ ID NO: 298, and is shown below:

Met Glu Ile Pro Val Pro Val Gln Pro Ser Trp Leu Arg Arg Ala Ser Ala Pro Leu Pro **Gly Leu Ser Ala Pro Gly Arg Leu Phe Asp Gln Arg Phe Gly Glu Gly Leu Leu Glu Ala Glu Leu Ala Ala Leu Cys Pro Thr Thr Leu Ala Pro Tyr Tyr Leu Arg Ala Pro Ser Val Ala Leu Pro Val Ala Gln Val Pro Thr Asp Pro Gly His Phe Ser Val Leu Leu Asp Val Lys His Phe Ser Pro Glu Glu Ile Ala Val Lys Val Val Gly Glu His Val Glu Val His Ala Arg His Glu Glu Arg Pro Asp Glu His Gly Phe Val Ala Arg Glu Phe His Arg Arg Tyr Arg Leu Pro Pro Gly Val Asp Pro Ala Ala Val Thr Ser Ala Leu Ser Pro Glu Gly Val Leu Ser Ile Gln Ala Ala Pro Ala Ser Ala Gln Ala Pro Pro Pro Ala Ala Ala Lys.**

The underlined residues represent amino acids 15-21.

X1 is 0-14 amino acids of SEQ ID NO: 298 between residues 1 and 14 of **SEQ ID NO:298** (shown in italics above). Thus, if X1 is 5 amino acids of residues 1 and 14 of **SEQ ID NO:298**, then X1 would be the 5 amino acids contiguous to residues 15-21, eg: SWLRR **(SEQ ID NO:303)**. Similarly, where X1 is the following number of amino acids of residues 1-14 of **SEQ ID NO:298**, its identity is as shown below:

1 amino acid of **SEQ ID NO:298:** R

2 amino acids of **SEQ ID NO:298:** RR
3 amino acids of **SEQ ID NO:298:** LRR (**SEQ ID NO: 304**)
4 amino acids of **SEQ ID NO:298:** WLRR (**SEQ ID NO: 1**)
6 amino acids of **SEQ ID NO:298:** PSWLRR (**SEQ ID NO: 305**)
7 amino acids of **SEQ ID NO:298:** NPSWLRR (**SEQ ID NO: 306**)
8 amino acids of **SEQ ID NO:298:** VNPSWLRR (**SEQ ID NO: 307**)
9 amino acids of **SEQ ID NO:298:** PVNPSWLRR (**SEQ ID NO: 308**)
10 amino acids of **SEQ ID NO:298:** VPVNPSWLRR (**SEQ ID NO: 309**)
11 amino acids of **SEQ ID NO:298:** PVPVNPSWLRR (**SEQ ID NO: 310**)
12 amino acids of **SEQ ID NO:298:** IPVPPVNPSWLRR (**SEQ ID NO: 311**)
13 amino acids of **SEQ ID NO:298:** EIPVPPVNPSWLRR (**SEQ ID NO: 312**)
14 amino acids of **SEQ ID NO:298:** MEIPVPPVNPSWLRR (**SEQ ID NO: 313**)

In a further embodiment, X1 is 0, 1, 2, 3, or 4 amino acids of the sequence WLRR (**SEQ ID NO:1**).

In one embodiment, X3 is 0-140 amino acids between residues 21 and 160 of **SEQ ID NO:298**. According to this embodiment, X3 can be 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139 or 140 amino acids between residues 21 and 160 of **SEQ ID NO:298**.

For example, if X3 is 5 amino acids between residues 21 and 160 of **SEQ ID NO:298**, then X3 would be the 5 amino acids contiguous to residues 15-21, eg: GLSAP (**SEQ ID NO: 314**). Other possible X3 sequences will be apparent to one of skill in the art based on the teachings provided herein.

In another embodiment, X3 is 0, 1, 2, or 3 amino acids of a sequence of genus Z1-Z2-Z3, wherein Z1 is selected from the group consisting of G and D;

Z2 is selected from the group consisting of L and K; and

Z3 is selected from the group consisting of S, T, and K.

For example, if X3 is 2 amino acids of a sequence of the genus Z1-Z2-Z3, then the possibilities for X3 are GL, GK, DL, and DK. Other possible X3 sequences in this embodiment will be apparent to one of skill in the art based on the teachings provided herein.

According to various embodiments of the polypeptides of general formula I, X2 is S, T, Y, D E, a phosphoserine mimic, or a phosphotyrosine mimic. It is preferred that X2 is S, T, or Y; more preferred that X2 is S or T, and most preferred that X2 is S. In these embodiments where X2 is S, T, or Y, it is most preferred that X2 is phosphorylated. When X2 is D or E, these residues have a negative charge that mimics the phosphorylated state. The polypeptides of general formula I are optimally effective in the methods of the invention when X2 is phosphorylated, is a phosphoserine or phosphotyrosine mimic, or is another mimic of a phosphorylated amino acid residue, such as a D or E residue. Examples of phosphoserine mimics include, but are not limited to, sulfoserine, amino acid mimics containing a methylene substitution for the phosphate oxygen, 4-phosphono(difluoromethyl)phenylanaline, and L-2-amino-4-(phosphono)-4,4-difuorobutanoic acid. Other phosphoserine mimics can be made by those of skill in the art. Examples of phosphotyrosine mimics include, but are not limited to, phosphonomethylphenylalanine, difluorophosphonomethylphenylalanine, fluoro-O-malonyltyrosine and O-malonyltyrosine.

In a preferred embodiment, the polypeptide according to the general formula comprises or consists of an amino acid sequence according to SEQ ID NO:300 (WLRRApSAPLPGL), wherein the "pS" represents a phosphorylated serine residue.

In another embodiment, the polypeptides according to general formula I may further comprise one or more molecules comprising an aromatic ring. In one such embodiment, the one or molecules comprising an aromatic ring are amino acids, such as any combination of 1-5 phenylalanine (F), tyrosine (Y), or tryptophan (W) residues. Thus, for example, the polypeptides according to general formula I can further comprise any combination of F, Y, and W, such as F, FF, Y, YY, W, WW, FY, FW, YF, YW, WY, WF, or a 3, 4, or 5 amino acid combination of F, Y, and W. In another embodiment, the molecule comprising an aromatic ring is one or more molecules comprising one or more aromatic rings that can optionally be substituted with halogen, lower alkyl, lower alkylthio, trifluoromethyl, lower acyloxy, aryl, and heteroaryl. For example, the one or more molecules comprising one or more aromatic ring may comprise 9-fluorenylmethyl

(Fm). Examples of such molecules include, but are not limited to 9-fluorenylmethylcarbonyl, 9-fluorenylmethylcarbamates, 9-fluorenylmethylcarbonates, 9-fluorenylmethyl esters, 9-fluorenylmethylphosphates, and S-9-fluorenylmethyl thioethers. In embodiments wherein the molecule comprising an aromatic ring is not an amino acid, it can be attached to the polypeptide by methods known in the art, including but not limited to, standard Fmoc protection chemistry employed in peptide synthesis.

Thus, according to these various embodiments, a representative sample of polypeptides according to general formula I for use in the methods of the invention include, but are not limited to, polypeptides comprising or consisting of the following sequences: (ASAPLP) **(SEQ ID NO:3)**; (ATAPLP) **(SEQ ID NO:4)**; (RASAPLP) **(SEQ ID NO:5)**; (RATAPLP) **(SEQ ID NO:6)**; (AYAPLP) **(SEQ ID NO:7)**; (RAYAPLP) **(SEQ ID NO:8)**;(RRASAPLP) **(SEQ ID NO:9)**; (LRRASAPLP) **(SEQ ID NO:10)**; (WLRRASAPLP); **(SEQ ID NO:11)** (RRATAPLP) **(SEQ ID NO:12)**; (LRRATAPLP) **(SEQ ID NO:13)**; (WLRRATAPLP) **(SEQ ID NO:14)**; (RRAYAPLP) **(SEQ ID NO:15)**; (LRRAYAPLP) **(SEQ ID NO:16)**; (WLRRAYAPLP) **(SEQ ID NO:17)**; (RRASAPLPG) **(SEQ ID NO:18)**; (RRASAPLPD) **(SEQ ID NO:19)**; (RRASAPLPGL) **(SEQ ID NO:20)**; (RRASAPLPGK) **(SEQ ID NO:21)**; (RRASAPLPDL) **(SEQ ID NO:22)**; (RRASAPLPDK) **(SEQ ID NO:23)**; (RRASAPLPGLS) **(SEQ ID NO:24)**; (RRASAPLPGLT) **(SEQ ID NO:25)**; (RRASAPLPGKS) **(SEQ ID NO:26)**; (RRASAPLPGKT) **(SEQ ID NO:27)**; (RRASAPLPDLS) **(SEQ ID NO:28)**; RRASAPLPDLT) **(SEQ ID NO:29)**; (RRASAPLPDKS) **(SEQ ID NO:30)**; (RRASAPLPDKT) **(SEQ ID NO:31)**; (LRRASAPLPG) **(SEQ ID NO:32)**; (LRRASAPLPD) **(SEQ ID NO:33)**; (LRRASAPLPGL) **(SEQ ID NO:34)**; (LRRASAPLPGK) **(SEQ ID NO:35)**; (LRRASAPLPDL) **(SEQ ID NO:36)**; (LRRASAPLPDK) **(SEQ ID NO:37)**; (LRRASAPLPGLS) **(SEQ ID NO:38)**; (LRRASAPLPGLT) **(SEQ ID NO:39)**; (LRRASAPLPGKS) **(SEQ ID NO:40)**; (LRRASAPLPGKT) **(SEQ ID NO:41)**; (LRRASAPLPDLS) **(SEQ ID NO:42)**; (LRRASAPLPDLT) **(SEQ ID NO:43)**; (LRRASAPLPDKS) **(SEQ ID NO:44)**; (LRRASAPLPDKT) **(SEQ ID NO:45)**; (WLRRASAPLPG) **(SEQ ID NO:46)**; (WLRRASAPLPD) **(SEQ ID NO:47)**; (WLRRASAPLPGL) **(SEQ ID NO:48)**; (WLRRASAPLPGK) **(SEQ ID NO:49)**; (WLRRASAPLPDL) **(SEQ ID NO:50)**; (WLRRASAPLPDK) **(SEQ ID NO:51)**; (WLRRASAPLPGLS) **(SEQ ID NO:52)**; (WLRRASAPLPGLT) **(SEQ ID NO:53)**;

(WLRRASAPLPGKS) (SEQ ID NO:54); (WLRRASAPLPGKT) (SEQ ID NO:55); (WLRRASAPLPDLS) (SEQ ID NO:56); (WLRRASAPLPDLT) (SEQ ID NO:57); (WLRRASAPLPDKS) (SEQ ID NO:58); (WLRRASAPLPDKT) (SEQ ID NO:59); (RRATAPLPG) (SEQ ID NO:60); (RRATAPLPD) (SEQ ID NO:61); (RRATAPLPGL) (SEQ ID NO:62); (RRATAPLPGK) (SEQ ID NO:63); (RRATAPLPDL) (SEQ ID NO:64); (RRATAPLPDK) (SEQ ID NO:65); (RRATAPLPGLS) (SEQ ID NO:66); (RRATAPLPGLT) (SEQ ID NO:67); (RRATAPLPGKS) (SEQ ID NO:68); (RRATAPLPGKT) (SEQ ID NO:69); (RRATAPLPDLS) (SEQ ID NO:70); (RRATAPLPDLT) (SEQ ID NO:71); (RRATAPLPDKS) (SEQ ID NO:72); (RRATAPLPDKT) (SEQ ID NO:73); (LRRATAPLPG) (SEQ ID NO:74); (LRRATAPLPD) (SEQ ID NO:75); (LRRATAPLPGL) (SEQ ID NO:76); (LRRATAPLPGK) (SEQ ID NO:77); (LRRATAPLPDL) (SEQ ID NO:78); (LRRATAPLPDK) (SEQ ID NO:79); (LRRATAPLPGLS) (SEQ ID NO:80); (LRRATAPLPGLT) (SEQ ID NO:81); (LRRATAPLPGKS) (SEQ ID NO:82); (LRRATAPLPGKT) (SEQ ID NO:83); (LRRATAPLPDLS) (SEQ ID NO:84); (LRRATAPLPDLT) (SEQ ID NO:85); (LRRATAPLPDKS) (SEQ ID NO:86); (LRRATAPLPDKT) (SEQ ID NO:87); (WLRRATAPLPG) (SEQ ID NO:88); (WLRRATAPLPD) (SEQ ID NO:89); (WLRRATAPLPGL) (SEQ ID NO:90); (WLRRATAPLPGK) (SEQ ID NO:91); (WLRRATAPLPDL) (SEQ ID NO:92); (WLRRATAPLPDK) (SEQ ID NO:93); (WLRRATAPLPGLS) (SEQ ID NO:94); (WLRRATAPLPGLT) (SEQ ID NO:95); (WLRRATAPLPGKS) (SEQ ID NO:96); (WLRRATAPLPGKT) (SEQ ID NO:97); (WLRRATAPLPDLS) (SEQ ID NO:98); (WLRRATAPLPDLT) (SEQ ID NO:99); (WLRRATAPLPDKS) (SEQ ID NO:100); (WLRRATAPLPDKT) (SEQ ID NO:101); (RRAYAPLPG) (SEQ ID NO:102); (RRAYAPLPD) (SEQ ID NO:103); (RRAYAPLPGL) (SEQ ID NO:104); (RRAYAPLPGK) (SEQ ID NO:105); (RRAYAPLPDL) (SEQ ID NO:106); (RRAYAPLPDK) (SEQ ID NO:107); (RRAYAPLPGLS) (SEQ ID NO:108); (RRAYAPLPGLT) (SEQ ID NO:109); (RRAYAPLPGKS) (SEQ ID NO:110; (RRAYAPLPGKT) (SEQ ID NO:111); (RRAYAPLPDLS) (SEQ ID NO:112); (RRAYAPLPDLT) (SEQ ID NO:113); (RRAYAPLPDKS) (SEQ ID NO:114); (RRAYAPLPDKT) (SEQ ID NO:115); (LRRAYAPLPG) (SEQ ID NO:116); (LRRAYAPLPD) (SEQ ID NO:117); (LRRAYAPLPGL) (SEQ ID NO:118); (LRRAYAPLPGK) (SEQ ID NO:119); (LRRAYAPLPDL) (SEQ ID NO:120);

(LRRAYAPLPDK) (SEQ ID NO:121); (LRRAYAPLPGLS) (SEQ ID NO:122); (LRRAYAPLPGLT) (SEQ ID NO:123); (LRRAYAPLPGKS) (SEQ ID NO:124); (LRRAYAPLPGKT) (SEQ ID NO:125); (LRRAYAPLPDLS) (SEQ ID NO:126); (LRRAYAPLPDLT) (SEQ ID NO:127); (LRRAYAPLPDKS) (SEQ ID NO:128); (LRRAYAPLPDKT) (SEQ ID NO:129); (WLRRAYAPLPG) (SEQ ID NO:130); (WLRRAYAPLPD) (SEQ ID NO:131); (WLRRAYAPLPGL) (SEQ ID NO:132); (WLRRAYAPLPGK) (SEQ ID NO:133); (WLRRAYAPLPDL) (SEQ ID NO:134); (WLRRAYAPLPDK) (SEQ ID NO:135); (WLRRAYAPLPGLS) (SEQ ID NO:136); (WLRRAYAPLPGLT) (SEQ ID NO:137); (WLRRAYAPLPGKS) (SEQ ID NO:138); (WLRRAYAPLPGKT) (SEQ ID NO:139); (WLRRAYAPLPDLS) (SEQ ID NO:140); (WLRRAYAPLPDLT) (SEQ ID NO:141); (WLRRAYAPLPDKS) (SEQ ID NO:142); and (WLRRAYAPLPDKT) (SEQ ID NO:143); ((F/Y/W)RRASAPLP) (SEQ ID NO:144); ((F/Y/W)LRRASAPLP) (SEQ ID NO:145); ((F/Y/W)WLRRASAPLP); (SEQ ID NO:146) ((F/Y/W)RRATAPLP) (SEQ ID NO:147); ((F/Y/W)LRRATAPLP) (SEQ ID NO:148); ((F/Y/W)WLRRATAPLP) (SEQ ID NO:149); ((F/Y/W)RRAYAPLP) (SEQ ID NO:150); ((F/Y/W)LRRAYAPLP) (SEQ ID NO:151); ((F/Y/W)WLRRAYAPLP) (SEQ ID NO:152); ((F/Y/W)RRASAPLPG) (SEQ ID NO:153); ((F/Y/W)RRASAPLPD) (SEQ ID NO:154); ((F/Y/W)RRASAPLPGL) (SEQ ID NO:155); ((F/Y/W)RRASAPLPGK) (SEQ ID NO:156); ((F/Y/W)RRASAPLPDL) (SEQ ID NO:157); $((F/Y/W)RRASAPLPDK)_1$ (SEQ ID NO:158); ((F/Y/W)RRASAPLPGLS) (SEQ ID NO:159); ((F/Y/W)RRASAPLPGLT) (SEQ ID NO:160); ((F/Y/W)RRASAPLPGKS); (SEQ ID NO:161); ((F/Y/W)RRASAPLPGKT) (SEQ ID NO:162); ((F/Y/W)RRASAPLPDLS) (SEQ ID NO:163); ((F/Y/W)RRASAPLPDLT) (SEQ ID NO:164); ((F/Y/W)RRASAPLPDKS) (SEQ ID NO:165); ((F/Y/W)RRASAPLPDKT) (SEQ ID NO:166); ((F/Y/W)LRRASAPLPG) (SEQ ID NO:167); ((F/Y/W)LRRASAPLPD) (SEQ ID NO:168); ((F/Y/W))LRRASAPLPGL) (SEQ ID NO:169); ((F/Y/W)LRRASAPLPGK) (SEQ ID NO:170); ((F/Y/W)LRRASAPLPDL) (SEQ ID NO:171); ((F/Y/W)LRRASAPLPDK) (SEQ ID NO:172); ((F/Y/W)LRRASAPLPGLS) (SEQ ID NO:173); ((F/Y/W)LRRASAPLPGLT) (SEQ ID NO:174); ((F/Y/W)LRRASAPLPGKS) (SEQ ID NO:175); ((F/Y/W)LRRASAPLPGKT) (SEQ ID NO:176); ((F/Y/W)LRRASAPLPDLS) (SEQ ID NO:177); ((F/Y/W)LRRASAPLPDLT) (SEQ ID NO:178); ((F/Y/W)LRRASAPLPDKS) (SEQ ID NO:179); ((F/Y/W)LRRASAPLPDKT) (SEQ ID

NO:180); ((F/Y/W)WLRRASAPLPG) (SEQ ID NO:181); ((F/Y/W)WLRRASAPLPD) (SEQ ID NO:182); ((F/Y/W)WLRRASAPLPGL) (SEQ ID NO:183); ((F/Y/W)WLRRASAPLPGK) (SEQ ID NO:184); ((F/Y/W)WLRRASAPLPDL) (SEQ ID NO:185); ((F/Y/W)WLRRASAPLPDK) (SEQ ID NO:186); ((F/Y/W)WLRRASAPLPGLS) (SEQ ID NO:187); ((F/Y/W)WLRRASAPLPGLT) (SEQ ID NO:188); ((F/Y/W)WLRRASAPLPGKS) (SEQ ID NO:189); ((F/Y/W)WLRRASAPLPGKT) (SEQ ID NO:190); ((F/Y/W)WLRRASAPLPDLS) (SEQ ID NO:191); ((F/Y/W)WLRRASAPLPDLT) (SEQ ID NO:192); ((F/Y/W)WLRRASAPLPDKS) (SEQ ID NO:193); ((F/Y/W)WLRRASAPLPDKT) (SEQ ID NO:194); ((F/Y/W)RRATAPLPG) (SEQ ID NO:195); ((F/Y/W)RRATAPLPD) (SEQ ID NO:196); ((F/Y/W)RRATAPLPGL) (SEQ ID NO:197); ((F/Y/W)RRATAPLPGK) (SEQ ID NO:198); ((F/Y/W)RRATAPLPDL) (SEQ ID NO:199); ((F/Y/W)RRATAPLPDK) (SEQ ID NO:200); ((F/Y/W)RRATAPLPGLS) (SEQ ID NO:201); ((F/Y/W)RRATAPLPGLT) (SEQ ID NO:202); ((F/Y/W)RRATAPLPGKS) (SEQ ID NO:203); ((F/Y/W)RRATAPLPGKT) (SEQ ID NO:204); ((F/Y/W)RRATAPLPDLS) (SEQ ID NO:205); ((F/Y/W)RRATAPLPDLT) (SEQ ID NO:206); ((F/Y/W)RRATAPLPDKS) (SEQ ID NO:207); ((F/Y/W)RRATAPLPDKT) (SEQ ID NO:208); ((F/Y/W)LRRATAPLPG) (SEQ ID NO:209); ((F/Y/W)LRRATAPLPD) (SEQ ID NO:210); ((F/Y/W)LRRATAPLPGL) (SEQ ID NO:211); ((F/Y/W)LRRATAPLPGK) (SEQ ID NO:212); ((F/Y/W)LRRATAPLPDL) (SEQ ID NO:213); ((F/Y/W)LRRATAPLPDK) (SEQ ID NO:214); ((F/Y/W)LRRATAPLPGLS) (SEQ ID NO:215); ((F/Y/W)LRRATAPLPGLT) (SEQ ID NO:216); ((F/Y/W)LRRATAPLPGKS) (SEQ ID NO:217); ((F/Y/W)LRRATAPLPGKT) (SEQ ID NO:218); ((F/Y/W)LRRATAPLPDLS) (SEQ ID NO:219); ((F/Y/W)LRRATAPLPDLT) (SEQ ID NO:220); ((F/Y/W)LRRATAPLPDKS) (SEQ ID NO:221); ((F/Y/W)LRRATAPLPDKT) (SEQ ID NO:222); ((F/Y/W)WLRRATAPLPG) (SEQ ID NO:223); ((F/Y/W)WLRRATAPLPD) (SEQ ID NO:224); ((F/Y/W)WLRRATAPLPGL) (SEQ ID NO:225); ((F/Y/W)WLRRATAPLPGK) (SEQ ID NO:226); ((F/Y/W)WLRRATAPLPDL) (SEQ ID NO:227); ((F/Y/W)WLRRATAPLPDK) (SEQ ID NO:228); ((F/Y/W)WLRRATAPLPGLS) (SEQ ID NO:229); ((F/Y/W)WLRRATAPLPGLT) (SEQ ID NO:230); ((F/Y/W)WLRRATAPLPGKS) (SEQ ID NO:231); ((F/Y/W)WLRRATAPLPGKT)

(SEQ ID NO:232); ((F/Y/W)WLRRATAPLPDLS) (SEQ ID NO:233); ((F/Y/W)WLRRATAPLPDLT) (SEQ ID NO:234); ((F/Y/W)WLRRATAPLPDKS) (SEQ ID NO:235); ((F/Y/W)WLRRATAPLPDKT) (SEQ ID NO:236); ((F/Y/W)RRAYAPLPG) (SEQ ID NO:237); ((F/Y/W)RRAYAPLPD) (SEQ ID NO:238); ((F/Y/W)RRAYAPLPGL) (SEQ ID NO:239); ((F/Y/W)RRAYAPLPGK) (SEQ ID NO:240); ((F/Y/W)RRAYAPLPDL) (SEQ ID NO:241); ((F/Y/W)RRAYAPLPDK) (SEQ ID NO:242); ((F/Y/W)RRAYAPLPGLS) (SEQ ID NO:243); ((F/Y/W)RRAYAPLPGLT) (SEQ ID NO:244); ((F/Y/W)RRAYAPLPGKS) (SEQ ID NO:245); ((F/Y/W)RRAYAPLPGKT) (SEQ ID NO:246); ((F/Y/W)RRAYAPLPDLS) (SEQ ID NO:247); ((F/Y/W)RRAYAPLPDLT) (SEQ ID NO:248); ((F/Y/W)RRAYAPLPDKS) (SEQ ID NO:249); ((F/Y/W)RRAYAPLPDKT) (SEQ ID NO:250); ((F/Y/W)LRRAYAPLPG) (SEQ ID NO:251); ((F/Y/W)LRRAYAPLPD) (SEQ ID NO:252); ((F/Y/W)LRRAYAPLPGL) (SEQ ID NO:253); ((F/Y/W)LRRAYAPLPGK) (SEQ ID NO:254); ((F/Y/W)LRRAYAPLPDL) (SEQ ID NO:255); ((F/Y/W)LRRAYAPLPDK) (SEQ ID NO:256); ((F/Y/W)LRRAYAPLPGLS) (SEQ ID NO:257); ((F/Y/W)LRRAYAPLPGLT) (SEQ ID NO:258); ((F/Y/W)LRRAYAPLPGKS) (SEQ ID NO:259); ((F/Y/W)LRRAYAPLPGKT) (SEQ ID NO:260); ((F/Y/W)LRRAYAPLPDLS) (SEQ ID NO:261); ((F/Y/W)LRRAYAPLPDLT) (SEQ ID NO:262); ((F/Y/W)LRRAYAPLPDKS) (SEQ ID NO:263); ((F/Y/W)LRRAYAPLPDKT) (SEQ ID NO:264); ((F/Y/W)WLRRAYAPLPG) (SEQ ID NO:265); ((F/Y/W)WLRRAYAPLPD) (SEQ ID NO:266); ((F/Y/W)WLRRAYAPLPGL) (SEQ ID NO:267); ((F/Y/W)WLRRAYAPLPGK) (SEQ ID NO:268); ((F/Y/W)WLRRAYAPLPDL) (SEQ ID NO:269); ((F/Y/W)WLRRAYAPLPDK) (SEQ ID NO:270); ((F/Y/W)WLRRAYAPLPGLS) (SEQ ID NO:271); ((F/Y/W)WLRRAYAPLPGLT) (SEQ ID NO:272); ((F/Y/W)WLRRAYAPLPGKS) (SEQ ID NO:273); ((F/Y/W)WLRRAYAPLPGKT) (SEQ ID NO:274); ((F/Y/W)WLRRAYAPLPDLS) (SEQ ID NO:275); ((F/Y/W)WLRRAYAPLPDLT) (SEQ ID NO:276); ((F/Y/W)WLRRAYAPLPDKS) (SEQ ID NO:277); and ((F/Y/W)WLRRAYAPLPDKT) (SEQ ID NO:278) wherein (F/Y/W) means that the residue is selected from F, Y, and W. Other specific polypeptides falling within the scope of general formula I will be readily apparent to one of skill in the art based on the teachings herein.

The polypeptides of general formula I may be present in multiple copies to provide increased efficacy for use in the methods of the invention. For example, the polypeptides may be present in 1, 2, 3, 4, or 5 copies. In a further embodiment, the polypeptides comprising a sequence according to general formula I comprise a combination of different sequences from the region X1-A(X2)APLP-X3. In this embodiment, for example, the polypeptide can consist of 1 copy of SEQ ID NO: 9 and 1 copy of SEQ ID NO: 143. In a different example, the polypeptide could consist of 2 copies of SEQID NO: 200 and 3 copies of SEQ ID NO: 62. It will be apparent to one of skill in the art that many such combinations are possible based on the teachings of the present invention.

In a preferred embodiment, the polypeptides according to general formula I further comprise one or more transduction domains. As used herein, the term "transduction domain" means an amino acid sequence that can carry the polypeptide across cell membranes. These domains can be linked to other polypeptides to direct movement of the linked polypeptide across cell membranes. In some cases the transducing molecules do not need to be covalently linked to the active polypeptide. In a preferred embodiment, the transduction domain is linked to the rest of the polypeptide via peptide bonding. Examples of such transduction domains include, but are not limited to $(R)_{4-9}$ **(SEQ ID NO:279)**; GRKKRRQRRRPPQ **(SEQ ID NO:280)**; YARAAARQARA **(SEQ ID NO:281)**; DAATATRGRSAASRPTERPRAPARSASRPRRPVE **(SEQ ID NO:282)**; GWTLNSAGYLLGLINLKALAALAKKIL **(SEQ ID NO:283)**; PLSSIFSRIGDP **(SEQ ID NO:284)**; AAVALLPAVLLALLAP **(SEQ ID NO:285)**; AAVLLPVLLAAP **(SEQ ID NO:286)**; VTVLALGALAGVGVG **(SEQ ID NO:287)**; GALFLGWLGAAGSTMGAWSQP **(SEQ ID NO:288)**; GWTLNSAGYLLGLINLKALAALAKKIL **(SEQ ID NO:289)**; KLALKLALKALKAALKLA **(SEQ ID NO:290)**; KETWWETWWTEWSQPKKKRKV **(SEQ ID NO:291)**; KAFAKLAARLYRKAGC **(SEQ ID NO:292)**; KAFAKLAARLYRAAGC **(SEQ ID NO:293)**; AAFAKLAARLYRKAGC **(SEQ ID NO:294)**; KAFAALAARLYRKAGC **(SEQ ID NO:295)**; KAFAKLAAQLYRKAGC **(SEQ ID NO:296)**, GGGGYGRKKRRQRRR **(SEQ ID NO:297)**, and YGRKKRRQRRR **(SEQ ID NO:299)**.

In a further embodiment, the polypeptides comprise or consist of polypeptides of the formula:

B1-X1-A(X2)APLP-X3-B2

wherein X1, X2, and X3 are as defined above, and wherein B1 and B2 are independently absent or comprise a transduction domain, as described above.

In a preferred embodiment, one or both of B1 and B2 comprise or consist of the amino acid sequence of YGRKKRRQRRR (**SEQ ID NO:299**) and/or YARAAARQARA (**SEQ ID NO:281**). In a most preferred embodiment, the polypeptide according to the general formulas disclosed herein comprises or consists of a polypeptide according to YGRKKRRQRRRWLRRApSAPLPGL (**SEQ ID NO:301**) or YARAAARQARAWLRRApSAPLPGL (**SEQ ID NO:315**), wherein "pS" represents a phosphorylated serine residue.

In a further embodiment of the methods of the present invention, the polypeptides comprise or consist of polypeptides of the formula:

J1-J2-X1-A(X2)APLP-X3-J3

wherein X1, X2, and X3 are as defined above, wherein J2 and J3 are independently absent or comprise a transduction domain, as described above, and wherein J1 is absent or is one or more molecules comprising one or more aromatic ring, as discussed above.

The polypeptides for use in the methods of the invention can further be derivatized to provide enhanced half-life, for example, by linking to polyethylene glycol. The polypeptides of the invention may comprise L-amino acids, D-amino acids (which are resistant to L-amino acid-specific proteases in vivo), a combination of D- and L-amino acids, and various "designer" amino acids (e.g., β-methyl amino acids, Cα-methyl amino acids, and Nα-methyl amino acids, etc.) to convey special properties. Synthetic amino acids include ornithine for lysine, and norleucine for leucine or isoleucine.

In addition, the polypeptides can have peptidomimetic bonds, such as ester bonds, to prepare polypeptides with novel properties. For example, a peptide may be generated that incorporates a reduced peptide bond, i.e., R_1-CH_2-NH-R_2, where R_1 and R_2 are amino acid residues or sequences. A reduced peptide bond may be introduced as a dipeptide subunit. Such polypeptides are resistant to protease activity, and possess an extended half-live in vivo.

The term "polypeptide" is used in its broadest sense to refer to a sequence of subunit amino acids, amino acid analogs, or peptidomimetics. The subunits are linked by peptide bonds, although the polypeptide can comprise further moieties that are not necessarily linked to the polypeptide by a peptide bond. For example, as discussed above, the polypeptide can further comprise a non-amino acid molecule that contains an aromatic ring.

The polypeptides described herein may be chemically synthesized or recombinantly expressed. Recombinant expression can be accomplished using standard methods in the art, generally involving the cloning of nucleic acid sequences capable of directing the expression of the polypeptides into an expression vector, which can be used to transfect or transduce a host cell in order to provide the cellular machinery to carry out expression of the polypeptides. Such expression vectors can comprise bacterial or viral expression vectors, and such host cells can be prokaryotic or eukaryotic.

Preferably, the polypeptides for use in the methods of the present invention are chemically synthesized. Synthetic polypeptides, prepared using the well-known techniques of solid phase, liquid phase, or peptide condensation techniques, or any combination thereof, can include natural and unnatural amino acids. Amino acids used for peptide synthesis may be standard Boc (Nα-amino protected Nα-t-butyloxycarbonyl) amino acid resin with the standard deprotecting, neutralization, coupling and wash protocols of standard solid phase procedure, or base-labile Nα-amino protected 9-fluorenylmethoxycarbonyl (Fmoc) amino acids. Both Fmoc and Boc Nα-amino protected amino acids can be obtained from Sigma, Cambridge Research Biochemical, or other chemical companies familiar to those skilled in the art. In addition, the polypeptides can be synthesized with other Nα-protecting groups that are familiar to those skilled in this art.

Solid phase peptide synthesis may be accomplished by techniques familiar to those in the art and provided, for example by using automated synthesizers.

As used herein, an "individual in need thereof" is an individual that has suffered or will suffer (for example, via a surgical procedure) a wound that may result in scar formation, or has resulted in scar formation. As used herein, the term "wound" refers broadly to injuries to the skin and subcutaneous tissue, but does not include wounds to blood vessels or heart tissue.

Such wounds include, but are not limited to lacerations; burns; punctures; pressure sores; bed sores; canker sores; trauma, bites; fistulas; ulcers; lesions caused by infections; periodontal wounds; endodontic wounds; burning mouth syndrome; laparotomy wounds; surgical wounds; incisional wounds; contractures after burns; tissue fibrosis, including but not limited to idiopathic pulmonary fibrosis, hepatic fibrosis, renal fibrosis, retroperitoneal fibrosis, and cystic fibrosis, but excluding blood vessel fibrosis or heart tissue fibrosis; and wounds resulting from cosmetic surgical procedures. As used herein, the phrase "reducing scar formation" means any decrease in scar formation that provides a therapeutic or cosmetic benefit to the patient. Such a therapeutic or cosmetic benefit can be achieved, for example, by decreasing the size and/or depth of a scar relative to scar formation in the absence of treatment with the methods of the invention, or by reducing the size of an existing scar.

As used herein, such scars include scars of all types, including but not limited to keloids; hypertrophic scars; and adhesion formation between organ surfaces, including but not limited to those occurring as a result of surgery.

The present invention, by providing methods for reducing scar formation, will be clinically useful for treating all types of wounds to reduce scar formation, both for reducing initial scar formation, and for therapeutic treatment of existing scars (i.e.: cutting out the scar after its formation, treating it with the compounds of the invention, and letting the scar heal more slowly). Such wounds are as described above. As used herein, the phrase "promoting wound healing" means any increase in wound healing that provides a therapeutic or cosmetic benefit to the patient. Such a therapeutic benefit can be achieved, for example, by one or more of increasing the rate of wound healing and/or increasing the degree of wound healing relative to an untreated individual. Such wounds are as described above.

In a preferred embodiment, the individual is a mammal; in a more preferred embodiment, the individual is a human.

While not being limited to a specific mechanism of action, the inventors believe that the beneficial effect of the methods of the invention in promoting wound healing and/or reducing scar formation are due to reduction of wound contraction within the wound area, which limits scar formation that accompanies wound healing, and increase in blood flow to the wound area.

As used herein, an "amount effective" of the one or more polypeptides is an amount that is sufficient to provide the intended benefit of treatment. An effective amount of the polypeptides that can be employed ranges generally between about 0.01 μg/kg body weight and about 10 mg/kg body weight, preferably ranging between about 0.05 μg/kg and about 5 mg/kg body weight. However dosage levels are based on a variety of factors, including the type of injury, the age, weight, sex, medical condition of the individual, the severity of the condition, the route of administration, and the particular compound employed. Thus, the dosage regimen may vary widely, but can be determined routinely by a physician using standard methods.

The polypeptides may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc.

For administration, the polypeptides are ordinarily combined with one or more adjuvants appropriate for the indicated route of administration. The compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, stearic acid, talc, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulphuric acids, acacia, gelatin, sodium alginate, polyvinylpyrrolidine, dextran sulfate, heparin-containing gels, and/or polyvinyl alcohol, and tableted or encapsulated for conventional administration. Alternatively, the compounds of this invention may be dissolved in saline, water, polyethylene glycol, propylene glycol, carboxymethyl cellulose colloidal solutions, ethanol, corn oil, peanut oil, cottonseed oil, sesame oil, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well known in the pharmaceutical art. The carrier or diluent may include time delay material, such as glyceryl monostearate or glyceryl distearate alone or with a wax, or other materials well known in the art.

The polypeptides or pharmaceutical compositions thereof may be administered by any suitable route, including orally, parentally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles. The term parenteral as used herein includes, subcutaneous, intravenous, intra-arterial, intramuscular, intrasternal, intratendinous, intraspinal, intracranial, intrathoracic, infusion techniques or intraperitoneally. Preferred embodiments for administration vary with respect to the condition being treated. In a preferred embodiment, the polypeptides or pharmaceutical compositions are disposed on or

in a wound dressing or other topical administration. Such wound dressings can be any used in the art, including but not limited to films (e.g., polyurethane films), hydrocolloids (hydrophilic colloidal particles bound to polyurethane foam), hydrogels (cross-linked polymers containing about at least 60% water), foams (hydrophilic or hydrophobic), calcium alginates (nonwoven composites of fibers from calcium alginate), cellophane, and biological polymers such as those described in US patent application publication number 20030190364, published October 9, 2003.

The polypeptides may be made up in a solid form (including granules, powders or suppositories) or in a liquid form (*e.g.*, solutions, suspensions, or emulsions). The polypeptides of the invention may be applied in a variety of solutions. Suitable solutions for use in accordance with the invention are sterile, dissolve sufficient amounts of the polypeptides, and are not harmful for the proposed application.

Example 1 Actin cytoskeleton disruption

Materials and Methods

Peptide synthesis and purification

Peptides were synthesized using standard f-moc chemistry and purified using high performance liquid chromatography (HPLC) by Cell Essentials (Boston, MA). Fluorescent peptides were synthesized with a fluorescein isothiocyanate (FITC) labeled on the N terminus, using β-alanine as a linker.

Cell culture, immunocytochemistry, and interference reflection microscopy

Unless otherwise stated, all reagents were purchased from Sigma, St. Louis, MO. Swiss Albino 3T3 fibroblasts (ATCC, Manassas, VA) were cultured in DMEM supplemented with 10% BCS, 4 mM L-glutamine and 50 μg/ml penicillin-streptomycin and maintained at 37°C, 5% CO_2. Cells were seeded and cultured overnight. Culture media was replaced with DMEM containing 0.5% BCS 1 hour prior to experimentation. Cells were incubated with the peptide analogues or reagent (LPA or forskolin) diluted in DMEM containing 0.5% BCS, 30 minutes at 37°C. Cells were then fixed in 4% paraformaldehyde, permeabilized in 0.25% Triton X-100, and blocked with 1% BSA solution for 1 hour. To determine f-actin cytoskeletal distribution, treated cells were incubated with Alexa 568 phalloidin

(Molecular Probes, Eugene, OR) in 1% BSA, 30 minutes. To determine focal adhesion protein localization, treated cells were incubated with primary monoclonal antibodies for α-actinin (1:100, Upstate, Charlottesville, VA), vinculin (1:100, Sigma) or paxillin (1:100, BD Bioscience-Transduction Labs, San Jose, CA) in 1% BSA solution for 2 hours, rinsed in PBS and incubated 60 min with Cy3-goat IgG secondary antibody (Jackson ImmunoResearch, West Grove, PA). Slides were mounted and analyzed by confocal microscopy (Leica TCS SP2, Bannockburn, IL). Interference reflection microscopy was used to determine the percentage of 3T3 cells positive for focal adhesions. Cells were cultured as described above and either untreated or treated with 100 nM Hep I (thrombospondin peptide), 10 μM and 25 μM pHSP20 (phospho HSP20 peptide) or 10 μM and 25μM sHSP20 (scrambled HSP20 peptide).

Results

Cellular processes such as cell adhesion, cytokinesis, cell motility, migration, and muscular contraction/relaxation require dynamic reorganization of the actin cytoskeleton. Activation of cyclic nucleotide signaling pathways in various cell types leads to profound alterations in the cytoskeleton, which include loss of central stress fibers and focal adhesion plaques; cytoplasmic retraction with the formation of thin processes; and rounding of the cell bodies (*1*). In aggregate, these changes lead to a star-shaped appearance that has been termed "stellation."

The cyclic nucleotide signaling pathways include adenylate cyclase/cAMP/cAMP-dependent protein kinase (PKA) and guanylate cyclase/cGMP/cGMP-dependent protein kinase (PKG). These pathways converge at the phosphorylation of the small heat shock-related protein, HSP20 on serine 16 (*2, 3*). To determine if HSP20 mediates cyclic nucleotide-dependent stellation, phosphopeptide analogues of HSP20 (pHSP20) were synthesized (*4*) that contained: 1) the amino acid sequence surrounding the phosphorylation site of HSP20 (WLRRApSAPLPGL) (**SEQ ID NO:300**); 2) a phosphoserine (pS); and 3) an 11 amino acid protein transduction domain from the HIV Tat protein (YGRKKRRQRRR). The sequence of the resulting test polypeptide is YGRKKRRQRRRWLRRApSAPLPGL (**SEQ ID NO:301**). Control peptides contained the same sequence as the phosphopeptide analogues except with either

an alanine in place of the phosphoserine (aHSP20) or a scrambled HSP20 sequence containing phosphoserine (scrHSP20, PRpSLWALGRPLSAK) (**SEQ ID NO:302**).

Swiss albino 3T3 cells were either untreated or treated with 10 μM LPA, 10 μM forskolin , 25 μM FITC-pHSP20, or 25 μM FITC-aHSP20 as described (*4*). Cells were fixed, stained for f-actin using Alexa 568 phalloidin, and visualized by projection images of confocal fluorescence microscopy. FITC-peptide flurescence was overlayed with actin staining to show colocalization. Cells that had been exposed to serum (10%) or lysophosphatidic acid (10 μM, 30 min) displayed robust stress fibers. Cells that were treated with the adenylate cyclase activator forskolin (10 μM, 30 min) or with pHSP20 displayed stellate morphology and disrupted stress fibers. The control peptide aHSP20 did not lead to alterations in morphology or stress fibers.

To confirm that the loss of stress fibers is associated with loss of filamentous (f-) actin and commensurate increases in globular (g-) actin, a DNase 1 inhibition assay was performed (*5*). 3T3 cells were cultured and treated as indicated (*4*). Monomer g-actin was biochemically quantitated using a DNase 1 inhibition assay. The level of g-actin in the cell extract that caused 50% inhibition of DNase 1 was estimated from a standard actin curve that was determined using known amounts of actin. Forskolin (10 μM, 30 min) and pHSP20 (25 μM, 30 min) treatment led to increases in g-actin (**Fig. 1**). Thus, transduction of pHSP20 led to similar changes in actin filament dynamics and cellular morphology, as did activation of the upstream adenylate cyclase activator forskolin.

To further verify disruption of the actin cytoskeletal network upon addition of pHSP20, the presence of focal adhesions was examined by interference reflection microscopy (*6, 7*). Focal adhesions are plaque-like scaffolds of both structural and signaling proteins that link the cytoskeleton to the extracellular matrix through integrin and syndecan receptors. Focal adhesions are formed in response to cell adhesion and involve signaling through Rho. These are dynamic structures that undergo disassembly and restructuring, characterized by loss of stress fibers and dispersion of vinculin, α-actinin, and paxillin, and are associated with increased cell motility. The matricellular proteins thrombospondin and tenascin-C cause focal adhesion disassembly and introduction of the intermediate cell adhesive state in a manner that requires basal PKG activity (*7*).

Swiss albino 3T3 cells were either untreated, or treated for 30 min with 10 μM LPA, 10 μM forskolin, 25 μM pHSP20 , 25 μM FITC-aHSP20, and immunostained for α-actinin, vinculin, or paxillin. Confocal projection images for FITC-peptides were overlayed with actin staining to show colocalization (f, i). Scale bar 50 μm.

Cells treated with forskolin or pHSP20 displayed a decrease in focal adhesion accumulations of α-actinin, vinculin, and paxillin, while cells treated with aHSP20 appeared to retain focal adhesion proteins. The pHSP20 led to disruption of focal adhesions in cultured 3T3 cells similar to the loss of focal adhesions that occurred with the hep I peptide of thrombospondin (**Fig. 2**), which has been shown to signal focal adhesion disassembly in a PKG-dependent manner (*7*). Again, aHSP20 had no effect on focal adhesions. These data suggest that phosphorylated HSP20 might be one of the downstream effectors by which PKG mediates focal adhesion disruption. These experiments further suggest that HSP20 and functionally equivalent polypeptides thereof, are useful for promoting wound healing and/or reducing scar formation.

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Example 2: Enhancing neural electrode durability

The durability of neural recording electrodes depends on scar formation. The scar formation in neural tissue is referred to as gliosis or glial scarring and results in insulation of the electrode from the neuronal tissues. These electrodes are often implanted into the brain for long-term monitoring of neuronal population activities for investigation of motor control or stimulation for treatment of neural trauma or diseases. In order to achieve the full potential of neural recording electrodes, methods must be developed to

reduce scar formation and improve the interface between the electrode and the electrically active neurons. The reduction of scar formation will improve both short- and long-term recording potential of the electrodes. Modulation of scar tissue formation around neural electrodes will improve function of stimulating electrodes as will including deep brain electrodes for Parkinson's disease, cochlear implants, and spinal cord stimulators. Since scar tissue acts as an insulator, improved conduction of action potentials to the electrodes will improve the performance of all implanted neural electrodes.

Neural Recording electrodes: Electrodes, when implanted into the brain, become encapsulated over time. Two biological responses result in encapsulation. The first involves the formation of a compact barrier of fibroblasts and extracellular matrix around the electrode. The second, gliosis, involves the glial cells of the brain. Gliosis is characterized by phenotypic modulation of astrocytes into glial cells, which produce extracellular matrix and further promote scar formation. There is a correlation between tissue trauma and degree of capsule formation with thicker capsules being formed in areas of higher tissue trauma. The increased trauma leads to disruption of the blood-brain barrier, which in turn, introduces blood-borne molecules into the brain. Glial scars, or capsules, can be up to 250 μm thick. These capsules act as insulators, impeding the conduction of electrical signals from neurons to the recording electrodes, thus limiting the function of the electrodes.

Inhibiting astrocyte proliferation and extracellular matrix formation around the site of electrodes will increase both the longevity and strength of the recording signals. Upon exposure to blood-borne factors, astrocytes exhibit morphological changes, which include stress fiber formation and loss of stellation. Stellation is a term used to describe alterations to the actin cytoskeleton that result in cells adopting a star-like or stellate shape. Upon loss of stellate morphology, astrocytes proliferate and secrete extracellular matrix proteins, which forms glial scars. Lysophosphatidic acid, a lipid found in high concentrations in blood, has been associated with the loss of stellate morphology, astrocytes proliferation, and gliosis.

Lysophosphatidic acid (LPA) is a biologically active signaling molecule that is bound to serum albumin in the blood. LPA can reverse stellation in astrocytes; this is likely due to inhibition of the cAMP pathway. LPA also can cause neurite retraction. HSP20 is the substrate molecule of both the cAMP and cGMP pathways and that its phosphorylation at serine 16 results in disruption of actin filaments.

Microwire arrays were implanted in the motor cortex of Sprague Dawley rats. Six male Sprague-Dawley rats (300-450g) were implanted with 2x4 arrays of 50μm tungsten wire. The electrodes were spaced 500 um apart for a total array size of approximately 1.5mm x 0.5mm. The implant was centered +3mm anterior and +2mm lateral from bregma. The craniotomy was opened slightly larger than the implant size and an injection (0.1 cc, 0.9 % PBS or 100 μm p20) was made into the arachnoid space near the implant site using a 30 gauge needle. The mirowire array was held in a micromanipulator and lowered 2mm from the surface of the dura. The craniotomy was covered with Gelfoam® and the implant and connector were cemented in place with dental acrylic. Three groups were implanted and evaluated histologically after four weeks. Group one was implanted with untreated electrodes. Group two was implanted with dextran coated microwire electrodes and group three was implanted with dextran coated electrodes and received a subdural injection of the HSP20 biomimetic peptide (YGRKKRRQRRRWLRRApSAPLPGL (**SEQ ID NO:301**). At 4 weeks two animals from each group were sacrificed for histology. Animals were anesthetized and perfused with PBS followed by formalin. The brain tissue was dissected from the skull and sectioned into 100 μM sections using a vibrotome. Sections were permeablizd with 0.05% triton and blocked with bovine serum albumin followed by probing with rabbit anti-glial fibrillary acidic protein (GFAP) for astrocytes and goat anti-microtubule associated protein 2 (MAP2) for axons. Texas Red labeled anti-Rabbit and Cy5 labeled antij-donkey secondary antibodies were used respectively for visualization.

While significant glial scarring was seen with neural electrodes alone at four weeks, reduced scarring was seen with dextran coated electrodes. For the electrodes implanted with the addition of the HSP20 biomimetic peptide, essentially no scarring was observed; in addition, a higher density of axons was seen in the vicinity of the microwire electrodes. This data suggests that the HSP20 peptide is effective at both inhibiting scarring around the electrodes and enhancing axon survival in the vicinity of the implant, and further suggest that HSP20 and functionally equivalent polypeptides thereof are useful for promoting wound healing and/or reducing scar formation.

We claim:

1. A method for reducing scar formation, comprising administering to an individual in need thereof an amount effective to reduce scar formation of a polypeptide comprising a sequence according general formula I:

X1-A(X2)APLP-X3

wherein X1 is 0-14 amino acids of the sequence of heat shock protein 20 between residues 1 and 14 of SEQ ID NO: 298;

X2 is selected from the group consisting of S, T, Y, D, E, hydroxylysine, hydroxyproline, phosphoserine analogs and phosphotyrosine analogs; and

X3 is selected from the group consisting of (a) 0-140 amino acids of heat shock protein 20 between residues 21 and 160 of SEQ ID NO:298; and (b) 0, 1, 2, or 3 amino acids of a sequence of genus Z1-Z2-Z3, wherein Z1 is selected from the group consisting of G and D;

Z2 is selected from the group consisting of L and K; and

Z3 is selected from the group consisting of S, T, and K.

2. The method of claim 1 wherein X1 is 0-14 amino acids of the sequence of heat shock protein 20 between residues 1 and 14 of SEQ ID NO: 298.

3. The method of claim 1 wherein the polypeptide comprises an amino acid sequence of SEQ ID NO:298.

4. The method of claim 1 wherein X2 is selected from the group consisting of S, T, and Y, and wherein X2 is phosphorylated.

5. The method of claim 4 wherein X2 is S.

6. The method of claim 1 wherein the polypeptide comprises a sequence according to SEQ ID NO:300.

7. The method of claim 1 wherein the polypeptide comprises a polypeptide of the formula:

B1-X1-A(X2)APLP-X3-B2

wherein X1, X2, and X3 are as defined above, and wherein B1 and B2 are independently absent or comprise a transduction domain, as described above.

8. The method of claim 7 wherein one or both of B1 and B2 comprises the amino acid sequence of SEQ ID NO:299 and/or SEQ ID NO:281.

9. The method of claim 1 wherein the polypeptide comprises a polypeptide of SEQ ID NO:301 or SEQ ID NO:315.

10. The method of claim 1 wherein the polypeptide comprises a polypeptide of the formula::

J1-J2-X1-A(X2)APLP-X3-J3

wherein X1, X2, and X3 are as defined above, wherein J2 and J3 are independently absent or comprise a transduction domain, and wherein J1 is absent or is one or more molecules comprising one or more aromatic ring.

11. The method of claim 1 wherein the individual in need thereof has a wound selected from the group consisting of lacerations; burns; punctures; pressure sores; bed sores; canker sores; trauma, bites; fistulas; ulcers; lesions caused by infections; periodontal wounds; endodontic wounds; burning mouth syndrome; laparotomy wounds; surgical wounds; incisional wounds; contractures after burns; tissue fibrosis; and wounds resulting from cosmetic surgical procedures

12. The method of claim 1 wherein the method is used for reducing initial scar formation.

13. A method for promoting wound healing, comprising administering to an individual in need thereof an amount effective to promote wound healing of a polypeptide comprising a sequence according general formula I:

X1-A(X2)APLP-X3

wherein X1 is 0-14 amino acids of the sequence of heat shock protein 20 between residues 1 and 14 of SEQ ID NO: 298;

X2 is selected from the group consisting of S, T, Y, D, E, hydroxylysine, hydroxyproline, phosphoserine analogs and phosphotyrosine analogs; and

X3 is selected from the group consisting of (a) 0-140 amino acids of heat shock protein 20 between residues 21 and 160 of SEQ ID NO:298; and (b) 0, 1, 2, or 3 amino acids of a sequence of genus Z1-Z2-Z3, wherein Z1 is selected from the group consisting of G and D;

Z2 is selected from the group consisting of L and K; and

Z3 is selected from the group consisting of S, T, and K.

14. The method of claim 13 wherein X1 is 0-14 amino acids of the sequence of heat shock protein 20 between residues 1 and 14 of SEQ ID NO: 298.

15. The method of claim 13 wherein the polypeptide comprises an amino acid sequence of SEQ ID NO:298.

16. The method of claim 13 wherein X2 is selected from the group consisting of S, T, and Y, and wherein X2 is phosphorylated.

17. The method of claim 16 wherein X2 is S.

18. The method of claim 13 wherein the polypeptide comprises a sequence according to SEQ ID NO:300.

19. The method of claim 13 wherein the polypeptide comprises a polypeptide of the formula:

B1-X1-A(X2)APLP-X3-B2

wherein X1, X2, and X3 are as defined above, and wherein B1 and B2 are independently absent or comprise a transduction domain, as described above.

20. The method of claim 19 wherein one or both of B1 and B2 comprises the amino acid sequence of SEQ ID NO:299 and/or SEQ ID NO:281.

21. The method of claim 13 wherein the polypeptide comprises a polypeptide of SEQ ID NO:301 or SEQ ID NO:315.

22. The method of claim 13 wherein the polypeptide comprises a polypeptide of the formula::

J1-J2-X1-A(X2)APLP-X3-J3

wherein X1, X2, and X3 are as defined above, wherein J2 and J3 are independently absent or comprise a transduction domain, and wherein J1 is absent or is one or more molecules comprising one or more aromatic ring.

23. The method of claim 13 wherein the individual in need thereof has a wound selected from the group consisting of lacerations; burns; punctures; pressure sores; bed sores; canker sores; trauma, bites; fistulas; ulcers; lesions caused by infections; periodontal wounds; endodontic wounds; burning mouth syndrome; laparotomy wounds; surgical wounds; incisional wounds; contractures after burns; tissue fibrosis; and wounds resulting from cosmetic surgical procedures

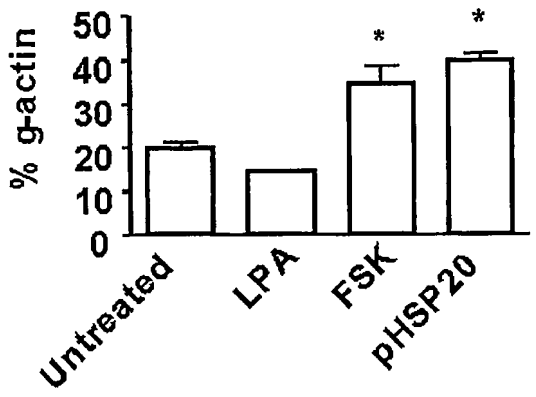

Figure 1: PhosphoHSP20 peptide disrupts the actin cytoskeleton.

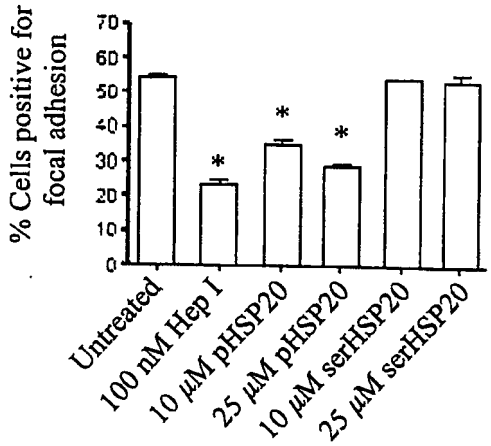

Figure 2: PhosphoHSP20 peptide disrupts focal adhesions.

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<400> 166

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<400> 183

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<400> 186

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<400> 189

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<400> 191

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<400> 196

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<400> 197

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<400> 200

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<400> 203

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<400> 209

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1 5 10

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<400> 210

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<400> 211

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<400> 212

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<400> 213

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<400> 215

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<400> 216

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<400> 217

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<400> 223

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1 5 10

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<400> 224

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<400> 225

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1 5 10

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<400> 226

Xaa Trp Leu Arg Arg Ala Thr Ala Pro Leu Pro Gly Lys
1 5 10

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<400> 227

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<400> 228

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<400> 229

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<400> 230

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<400> 231

Xaa Trp Leu Arg Arg Ala Thr Ala Pro Leu Pro Gly Lys Ser
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<400> 232

Xaa Trp Leu Arg Arg Ala Thr Ala Pro Leu Pro Gly Lys Thr
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<400> 233

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<400> 234

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<400> 235

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1 5 10

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<400> 236

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1 5 10

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<400> 237

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1 5 10

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<400> 238

Xaa Arg Arg Ala Tyr Ala Pro Leu Pro Asp
1 5 10

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<400> 239

Xaa Arg Arg Ala Tyr Ala Pro Leu Pro Gly Leu
1 5 10

<210> 240
<211> 11
<212> PRT
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<220>
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<220>
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<223> X stands for any of F, Y, or W.

<400> 240

Xaa Arg Arg Ala Tyr Ala Pro Leu Pro Gly Lys
1 5 10

<210> 241
<211> 11
<212> PRT
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<220>
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<220>
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<223> X stands for any of F, Y, or W.

<400> 241

Xaa Arg Arg Ala Tyr Ala Pro Leu Pro Asp Leu
1 5 10

<210> 242
<211> 11
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<220>
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<220>
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<223> X stands for any of F, Y, or W.

<400> 242

Xaa Arg Arg Ala Tyr Ala Pro Leu Pro Asp Lys
1 5 10

<210> 243
<211> 12
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<220>
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<220>
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<223> X stands for any of F, Y, or W.

<400> 243

Xaa Arg Arg Ala Tyr Ala Pro Leu Pro Gly Leu Ser
1 5 10

<210> 244
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<220>
<221> misc_feature
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<223> X stands for any of F, Y, or W.

<400> 244

Xaa Arg Arg Ala Tyr Ala Pro Leu Pro Gly Leu Thr
1 5 10

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<220>
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<400> 245

Xaa Arg Arg Ala Tyr Ala Pro Leu Pro Gly Lys Ser
1 5 10

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<400> 246

Xaa Arg Arg Ala Tyr Ala Pro Leu Pro Gly Lys Thr
1 5 10

<210> 247
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<220>
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<220>
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<223> X stands for any of F, Y, or W.

<400> 247

Xaa Arg Arg Ala Tyr Ala Pro Leu Pro Asp Leu Ser
1 5 10

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<220>
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<223> X stands for any of F, Y, or W.

<400> 248

Xaa Arg Arg Ala Tyr Ala Pro Leu Pro Asp Leu Thr
1 5 10

<210> 249
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<220>
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<220>
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<400> 249

Xaa Arg Arg Ala Tyr Ala Pro Leu Pro Asp Lys Ser
1 5 10

<210> 250

<211> 12
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<220>
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<220>
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<223> X stands for any of F, Y, or W.

<400> 250

Xaa Arg Arg Ala Tyr Ala Pro Leu Pro Asp Lys Thr
1 5 10

<210> 251
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<212> PRT
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<220>
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<400> 251

Xaa Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly
1 5 10

<210> 252
<211> 11
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<220>
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<220>
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<223> X stands for any of F, Y, or W.

<400> 252

Xaa Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp
1 5 10

<210> 253
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<212> PRT
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<220>
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<220>
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<222> (1)..(1)
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<400> 253

Xaa Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Leu
1 5 10

<210> 254
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<223> X stands for any of F, Y, or W.

<400> 254

Xaa Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Lys
1 5 10

<210> 255
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<400> 255

Xaa Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Leu
1 5 10

<210> 256
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<220>
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<400> 256

Xaa Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Lys
1 5 10

<210> 257
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<220>
<223> Derived sequence

<220>
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<400> 257

Xaa Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Leu Ser
1 5 10

<210> 258
<211> 13
<212> PRT
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<220>
<223> Derived sequence

<220>
<221> misc_feature
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<223> X stands for any of F, Y, or W.

<400> 258

Xaa Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Leu Thr
1 5 10

<210> 259
<211> 13
<212> PRT
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<220>
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<220>
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<222> (1)..(1)
<223> X stands for any of F, Y, or W.

<400> 259

Xaa Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Lys Ser
1 5 10

<210> 260
<211> 13

<212> PRT
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<220>
<223> Derived sequence

<220>
<221> misc_feature
<222> (1)..(1)
<223> X stands for any of F, Y, or W.

<400> 260

Xaa Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Lys Thr
1 5 10

<210> 261
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<213> Artificial Sequence

<220>
<223> Derived sequence

<220>
<221> misc_feature
<222> (1)..(1)
<223> X stands for any of F, Y, or W.

<400> 261

Xaa Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Leu Ser
1 5 10

<210> 262
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
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<220>
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<222> (1)..(1)
<223> X stands for any of F, Y, or W.

<400> 262

Xaa Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Leu Thr
1 5 10

<210> 263
<211> 13
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<213> Artificial Sequence

<220>
<223> Derived sequence

<220>

<221> misc_feature
<222> (1)..(1)
<223> X stands for any of F, Y, or W.

<400> 263

Xaa Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Lys Ser
1 5 10

<210> 264
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<213> Artificial Sequence

<220>
<223> Derived sequence

<220>
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<223> X stands for any of F, Y, or W.

<400> 264

Xaa Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Lys Thr
1 5 10

<210> 265
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<223> X stands for any of F, Y, or W.

<400> 265

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly
1 5 10

<210> 266
<211> 12
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<223> X stands for any of F, Y, or W.

<400> 266

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp
1 5 10

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<220>
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<223> X stands for any of F, Y, or W.

<400> 267

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Leu
1 5 10

<210> 268
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<222> (1)..(1)
<223> X stands for any of F, Y, or W.

<400> 268

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Lys
1 5 10

<210> 269
<211> 13
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<400> 269

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Leu
1 5 10

<210> 270
<211> 13
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<221> misc_feature
<222> (1)..(1)
<223> X stands for any of F, Y, or W.

<400> 270

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Lys
1 5 10

<210> 271
<211> 14
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<220>
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<220>
<221> misc_feature
<222> (1)..(1)
<223> X stands for any of F, Y, or W.

<400> 271

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Leu Ser
1 5 10

<210> 272
<211> 14
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<213> Artificial Sequence

<220>
<223> Derived sequence

<220>
<221> misc_feature
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<223> X stands for any of F, Y, or W.

<400> 272

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Leu Thr
1 5 10

<210> 273
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived sequence

<220>
<221> misc_feature

<222> (1)..(1)
<223> X stands for any of F, Y, or W.

<400> 273

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Lys Ser
1 5 10

<210> 274
<211> 14
<212> PRT
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<220>
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<220>
<221> misc_feature
<222> (1)..(1)
<223> X stands for any of F, Y, or W.

<400> 274

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Lys Thr
1 5 10

<210> 275
<211> 14
<212> PRT
<213> Artificial Sequence

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<220>
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<223> X stands for any of F, Y, or W.

<400> 275

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Leu Ser
1 5 10

<210> 276
<211> 14
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<213> Artificial Sequence

<220>
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<220>
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<222> (1)..(1)
<223> X stands for any of F, Y, or W.

<400> 276

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Leu Thr

1 5 10

<210> 277
<211> 14
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<220>
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<222> (1)..(1)
<223> X stands for any of F, Y, or W.

<400> 277

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Lys Ser
1 5 10

<210> 278
<211> 14
<212> PRT
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<220>
<223> Derived sequence

<220>
<221> misc_feature
<222> (1)..(1)
<223> X stands for any of F, Y, or W.

<400> 278

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Lys Thr
1 5 10

<210> 279
<211> 9
<212> PRT
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<220>
<223> Derived sequence

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<222> (5)..(9)
<223> Residues 5 through 9 are optionally absent.

<400> 279

Arg Arg Arg Arg Arg Arg Arg Arg Arg
1 5

<210> 280
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived sequence

<400> 280

Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Pro Pro Gln
1 5 10

<210> 281
<211> 11
<212> PRT
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<220>
<223> Derived sequence

<400> 281

Tyr Ala Arg Ala Ala Ala Arg Gln Ala Arg Ala
1 5 10

<210> 282
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived sequence

<400> 282

Asp Ala Ala Thr Ala Thr Arg Gly Arg Ser Ala Ala Ser Arg Pro Thr
1 5 10 15

Glu Arg Pro Arg Ala Pro Ala Arg Ser Ala Ser Arg Pro Arg Arg Pro
20 25 30

Val Glu

<210> 283
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived sequence

<400> 283

Gly Trp Thr Leu Asn Ser Ala Gly Tyr Leu Leu Gly Leu Ile Asn Leu
1 5 10 15

Lys Ala Leu Ala Ala Leu Ala Lys Lys Ile Leu
20 25

<210> 284
<211> 12
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<213> Artificial Sequence

<220>
<223> Derived sequence

<400> 284

Pro Leu Ser Ser Ile Phe Ser Arg Ile Gly Asp Pro
1 5 10

<210> 285
<211> 16
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<220>
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<400> 285

Ala Ala Val Ala Leu Leu Pro Ala Val Leu Leu Ala Leu Leu Ala Pro
1 5 10 15

<210> 286
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<212> PRT
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<220>
<223> Derived sequence

<400> 286

Ala Ala Val Leu Leu Pro Val Leu Leu Ala Ala Pro
1 5 10

<210> 287
<211> 15
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<220>
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<400> 287

Val Thr Val Leu Ala Leu Gly Ala Leu Ala Gly Val Gly Val Gly
1 5 10 15

<210> 288
<211> 21
<212> PRT
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<400> 288

Gly Ala Leu Phe Leu Gly Trp Leu Gly Ala Ala Gly Ser Thr Met Gly
1 5 10 15

Ala Trp Ser Gln Pro
20

<210> 289
<211> 27
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<220>
<223> Derived sequence

<400> 289

Gly Trp Thr Leu Asn Ser Ala Gly Tyr Leu Leu Gly Leu Ile Asn Leu
1 5 10 15

Lys Ala Leu Ala Ala Leu Ala Lys Lys Ile Leu
20 25

<210> 290
<211> 18
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<213> Artificial Sequence

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<400> 290

Lys Leu Ala Leu Lys Leu Ala Leu Lys Ala Leu Lys Ala Ala Leu Lys
1 5 10 15

Leu Ala

<210> 291
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<400> 291

Lys Glu Thr Trp Trp Glu Thr Trp Trp Thr Glu Trp Ser Gln Pro Lys
1 5 10 15

Lys Lys Arg Lys Val
20

<210> 292
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<220>
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<400> 292

Lys Ala Phe Ala Lys Leu Ala Ala Arg Leu Tyr Arg Lys Ala Gly Cys
1 5 10 15

<210> 293
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<400> 293

Lys Ala Phe Ala Lys Leu Ala Ala Arg Leu Tyr Arg Ala Ala Gly Cys
1 5 10 15

<210> 294
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<400> 294

Ala Ala Phe Ala Lys Leu Ala Ala Arg Leu Tyr Arg Lys Ala Gly Cys
1 5 10 15

<210> 295
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Lys Ala Phe Ala Ala Leu Ala Ala Arg Leu Tyr Arg Lys Ala Gly Cys
1 5 10 15

<210> 296
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<400> 296

Lys Ala Phe Ala Lys Leu Ala Ala Gln Leu Tyr Arg Lys Ala Gly Cys
1 5 10 15

<210> 297
<211> 15
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<400> 297

Gly Gly Gly Gly Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg
1 5 10 15

<210> 298
<211> 160
<212> PRT
<213> Homo sapiens

<400> 298

Met Glu Ile Pro Val Pro Val Gln Pro Ser Trp Leu Arg Arg Ala Ser
1 5 10 15

Ala Pro Leu Pro Gly Leu Ser Ala Pro Gly Arg Leu Phe Asp Gln Arg
20 25 30

Phe Gly Glu Gly Leu Leu Glu Ala Glu Leu Ala Ala Leu Cys Pro Thr
35 40 45

Thr Leu Ala Pro Tyr Tyr Leu Arg Ala Pro Ser Val Ala Leu Pro Val
50 55 60

Ala Gln Val Pro Thr Asp Pro Gly His Phe Ser Val Leu Leu Asp Val
65 70 75 80

Lys His Phe Ser Pro Glu Glu Ile Ala Val Lys Val Val Gly Glu His
85 90 95

Val Glu Val His Ala Arg His Glu Glu Arg Pro Asp Glu His Gly Phe
100 105 110

Val Ala Arg Glu Phe His Arg Arg Tyr Arg Leu Pro Pro Gly Val Asp
115 120 125

Pro Ala Ala Val Thr Ser Ala Leu Ser Pro Glu Gly Val Leu Ser Ile
130 135 140

Gln Ala Ala Pro Ala Ser Ala Gln Ala Pro Pro Pro Ala Ala Ala Lys
145 150 155 160

<210> 299
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived sequence

<400> 299

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg
1 5 10

<210> 300
<211> 12
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<220>
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<220>
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<222> (6)..(6)
<223> Ser residue is phosphorylated.

<400> 300

Trp Leu Arg Arg Ala Ser Ala Pro Leu Pro Gly Leu
1 5 10

<210> 301
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived sequence

<220>
<221> misc_feature
<222> (17)..(17)
<223> Ser residue is phosphorylated.

<400> 301

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Trp Leu Arg Arg Ala
1 5 10 15

Ser Ala Pro Leu Pro Gly Leu
20

<210> 302
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived sequence

<220>
<221> misc_feature
<222> (3)..(3)
<223> Ser residue is phosphorylated.

<400> 302

Pro Arg Ser Leu Trp Ala Leu Gly Arg Pro Leu Ser Ala Lys
1 5 10

<210> 303

<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived sequence

<400> 303

Ser Trp Leu Arg Arg
1 5

<210> 304
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived sequence

<400> 304

Leu Arg Arg
1

<210> 305
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived sequence

<400> 305

Pro Ser Trp Leu Arg Arg
1 5

<210> 306
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived sequence

<400> 306

Asn Pro Ser Trp Leu Arg Arg
1 5

<210> 307
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived sequence

<400> 307

Val Asn Pro Ser Trp Leu Arg Arg
1 5

<210> 308
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived sequence

<400> 308

Pro Val Asn Pro Ser Trp Leu Arg Arg
1 5

<210> 309
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived sequence

<400> 309

Val Pro Val Asn Pro Ser Trp Leu Arg Arg
1 5 10

<210> 310
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived sequence

<400> 310

Pro Val Pro Val Asn Pro Ser Trp Leu Arg Arg
1 5 10

<210> 311
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived sequence

<400> 311

Ile Pro Val Pro Pro Val Asn Pro Ser Trp Leu Arg Arg
1 5 10

<210> 312
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived sequence

<400> 312

Glu Ile Pro Val Pro Pro Val Asn Pro Ser Trp Leu Arg Arg
1 5 10

<210> 313
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived sequence

<400> 313

Met Glu Ile Pro Val Pro Pro Val Asn Pro Ser Trp Leu Arg Arg
1 5 10 15

<210> 314
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived sequence

<400> 314

Gly Leu Ser Ala Pro
1 5

<210> 315
<211> 23
<212> PRT
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<220>
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<220>
<221> misc_feature
<222> (17)..(17)
<223> Ser residue is phosphorylated.

<400> 315

Tyr Ala Arg Ala Ala Ala Arg Gln Ala Arg Ala Trp Leu Arg Arg Ala
1 5 10 15

Ser Ala Pro Leu Pro Gly Leu
20

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/004999

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/17 A61P17/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, BIOSIS, EMBASE, PASCAL, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 03/018758 A (KOMALAVILAS PADMINI ; BROPHY COLLEEN (US); LOKESH JOSHI (US); PANITCH) 6 March 2003 (2003-03-06) claims 1-72	1-23
P,A	TESSIER DERON J ET AL: "The small heat shock protein (HSP) 20 is dynamically associated with the actin cross-linking protein actinin." THE JOURNAL OF SURGICAL RESEARCH. 1 MAY 2003, vol. 111, no. 1, 1 May 2003 (2003-05-01), pages 152-157, XP001182463 ISSN: 0022-4804 the whole document	1-23

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 July 2004	22/07/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Fayos, C

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Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/004999

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	PARMITER CATHERINE MARGARET ET AL: "Protein transduction of biomimetic peptides leads to changes in the actin cytoskeleton of 3T3 cells." FASEB JOURNAL, vol. 17, no. 4-5, March 2003 (2003-03), pages Abstract No. 599.6 URL-http://ww, XP009033553 & FASEB MEETING ON EXPERIMENTAL BIOLOGY: TRANSLATING THE GENOME; SAN DIEGO, CA, USA; APRIL 11-15, 2003 ISSN: 0892-6638 abstract	1-23
A	BROPHY C M ET AL: "The small heat shock-related protein-20 is an actin-associated protein." JOURNAL OF VASCULAR SURGERY : OFFICIAL PUBLICATION, THE SOCIETY FOR VASCULAR SURGERY 'AND! INTERNATIONAL SOCIETY FOR CARDIOVASCULAR SURGERY, NORTH AMERICAN CHAPTER. FEB 1999, vol. 29, no. 2, February 1999 (1999-02), pages 326-333, XP009033572 ISSN: 0741-5214 the whole document	1-23

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/004999

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-23 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III *Observations where unity of invention is lacking (Continuation of item 3 of first sheet)*

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2004/004999

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03018758 A	06-03-2003	CA 2458574 A1	06-03-2003
		WO 03018758 A2	06-03-2003
		US 2003060399 A1	27-03-2003